Antibacterial chemotherapy principles of use

DR \ Nshwan Mansoor

DR \ Nashwan Mansoor

Antibacterial agents

A. BETA-LACTAM ANTIBIOTICS :- THEY ARE CLASSIFIED TO :-

1. Penicillin's

- **Natural penicillin's: benzylpenicillin, phenoxymethylpenicillin**
- **Penicillinase-resistant penicillin's: methicillin, flucloxacillin, nafcillin, oxacillin**
- **Aminopenicillins: ampicillin, amoxicillin**
- **Carboxy- and ureidopenicillins: ticarcillin, piperacillin, temocillin**

2. Cephalosporins

3. Monobactams

- Aztreonam

4. Carbapenems

- Imipenem, meropenem, ertapenem, doripenem

Antibacterial agents

A. Beta-lactam antibiotics :-

- A bactericidal action by inhibiting enzymes involved in cell wall synthesis.

Pharmacokinetics

- Good drug levels are achieved in lung, kidney, bone, muscle and liver, and in pleural, synovial, pericardial and peritoneal fluids.

- CSF levels are low, except when meninges are inflamed.

- Activity is not inhibited in abscess.

- Beta-lactams are activity is reduced in the presence of a high organism burden.

- Generally safe in pregnancy (except imipenem/cilastatin).

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Antibacterial agents

A. Beta-lactam antibiotics :-

❑ Adverse effects

- Immediate (IgE-mediated) allergic reactions are rare but life-threatening.
- Approximately 90% of patients who report a penicillin allergy do not have a true IgE-mediated allergy.
- Other reactions, such as rashes, fever and hematological effects (e.g. low white cell count), usually follow more prolonged therapy (more than 2 weeks).
- The relationship between allergy to penicillin and allergy to cephalosporins depends on the specific cephalosporin used.

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Antibacterial agents

A. Beta-lactam antibiotics :-

❑ Adverse effects

- Significant cross-reactivity with first-generation cephalosporins but cross-reactivity to second-/ third-generation cephalosporins is less common.
- Avoidance of cephalosporins, however, is recommended in patients who have IgE-mediated penicillin allergy.
- Cross-reactivity between penicillin and carbapenems is rare and carbapenems may be administered if there are no suitable alternatives and appropriate resuscitation facilities are available.

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Antibacterial agents

A. Beta-lactam antibiotics :-

❑ Adverse effects

- The monobactam aztreonam is the β-lactam least likely to cross-react in patients with penicillin allergy.

- Gastrointestinal upset and diarrhea are common, and a mild reversible hepatitis is recognized with many β-lactams.

- More severe forms of hepatitis can be observed with flucloxacillin and co-amoxiclav. Leucopenia, thrombocytopenia, coagulation.

Antibacterial agents

A. Beta-lactam antibiotics :-

1. Penicillin's

- Natural penicillin's :-

- Primarily effective against Gram-positive organisms (except staphylococci) and anaerobic organisms.

- Strep. pyogenes has remained sensitive to natural penicillin's worldwide.

- Carboxypenicillins (e.g. ticarcillin) and ureidopenicillins (e.g. piperacillin) :-

- **Active against Gram-negative organisms, especially Pseudomonas spp..**

- **Beta-lactamase inhibitors may be added to extend their spectrum of activity (e.g. piperacillin–tazobactam).**

- **Temocillin; it has good activity against Enterobacteriaceae, but poor activity against Pseudomonas aeruginosa and Gram positive bacteria.**

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Antibacterial agents

A. Beta-lactam antibiotics :-

1. Penicillin's

- Penicillinase-resistant penicillin's :-

- The mainstay of treatment for infections with Staph. aureus, other than MRSA.

- Aminopenicillins :-

- Have the same spectrum of activity as the natural penicillin's, with additional Gram-negative cover against Enterobacteriaceae.

- Amoxicillin has better oral absorption than ampicillin.
- No longer appropriate for empirical use in Gram-negative infections.

- In many organisms, resistance is due to β-lactamase production, which can be overcome by the addition of β-lactamase inhibitors (clavulanic acid or sulbactam).

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Antibacterial agents

A. Beta-lactam antibiotics :-

2. Cephalosporins and cephamycin's :-

- Cephalosporins are broad-spectrum agents..
- The group has no activity against enterococci except of ceftobiprole.
- Only the cephamycin's have anti-anaerobic activity.
- All cephalosporins are inactivated by ESBL.
- The spectrum of cephalosporins has also been enhanced by adding β-lactamase inhibitors
- Cephalosporins are arranged in generations.

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Antibacterial agents

First generation
- **Cefalexin, cefradine (oral)**
- **Cefazolin (IV)**

Second generation
- Cefuroxime (oral/IV)
- Cefaclor (oral)
- Cefoxitin (IV)

Third generation
- Cefixime (oral)
- Cefotaxime (IV)
- Ceftriaxone (IV)
- Ceftazidime (IV)

Fourth generation
- Cefepime (IV)

Fifth generation (also referred to as 'next generation')
- Ceftobiprole (IV) ceftaroline (IV)

Antibacterial agents

A. Beta-lactam antibiotics :-

2. Cephalosporins and cephamycin's :-

- **First-generation :-**

- Have excellent activity against Gram-positive organisms and some activity against Gram-negatives.

- **Second-generation :-**

- Drugs less retain Gram-positive activity but have extended Gram-negative activity.
- Cefoxitin, are active against anaerobic Gram-negative bacilli.

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Antibacterial agents

A. Beta-lactam antibiotics :-

2. Cephalosporins and cephamycin's :-

- **Third-generation agents :-**

- Anti-Gram negative cover.
- Ceftazidime, this is extended to include Pseudomonas spp.
- Cefotaxime and ceftriaxone have excellent Gram-negative activity and retain good activity against *Strep. pneumoniae* and β-hemolytic streptococci.
- Ceftriaxone is administered once daily and is therefore a suitable agent for outpatient intravenous (parenteral) antimicrobial therapy (OPAT).

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Antibacterial agents

A. Beta-lactam antibiotics :-

2. Cephalosporins and cephamycin's :-

- **Fourth-generation agents, e.g. cefepime :-**
  - **Have a broad spectrum of activity, including streptococci and some Gram-negatives, including P. aeruginosa.**

- **Fifth-generation agents, such as ceftobiprole and Ceftaroline :-**
  - **have an enhanced spectrum of Gram-positive activity that includes MRSA.**

  - **Have activity against Gram-negative bacteria.**

  - **Ceftobiprole, are active against P. aeruginosa.**

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Antibacterial agents

A. Beta-lactam antibiotics :-

3. Monobactams :-

- Aztreonam is the only available monobactam.
- Active against Gram-negative bacteria.
- Inactive against Gram-positive organisms or anaerobes.
- A parenteral-only agent and may be used safely in most penicillin-allergic patients other than those with an allergy to ceftazidime, which shares a common side chain with aztreonam.

4. Carbapenems :-

- These intravenous agents have the broadest antibiotic activity of the β-lactam antibiotics, covering most clinically significant bacteria, including anaerobes.

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Antibacterial agents

B. Macrolide and lincosamides :-

- Macrolides (e.g. erythromycin, clarithromycin and azithromycin) and lincosamides (e.g. clindamycin)
- Are bacteriostatic agents.
- Both classes bind to the same component of the ribosome, so they are not administered together.
- Macrolides are used for *Legionella*, *Mycoplasma*, *Chlamydia* and *Bordetella* infections.
- Azithromycin is employed for single-dose/short-course therapy for genitourinary *Chlamydia/Mycoplasma* spp. infections.
- Clindamycin is used primarily for skin, soft tissue, bone and joint infections.

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Antibacterial agents

B. Macrolide and lincosamides :-

- **Pharmacokinetics**
- **Macrolides**
- **Variable bioavailability (intravenous and oral preparations available).**
- **Frequency of administration: erythromycin is administered 4 times daily clarithromycin twice daily, azithromycin once daily.**
- **High protein binding, and excellent intracellular accumulation.**
- **Lincosamides (e.g. clindamycin)**
- **Good oral bioavailability.**
- **Food has no effect on absorption.**
- **Good bone/joint penetration, limited CSF penetration.**

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Antibacterial agents

B. Macrolide and lincosamides :-

❑ Adverse effects

- Gastrointestinal upset, especially in young adults (erythromycin 30%).
- Cholestatic jaundice with erythromycin isolate.
- Prolongation of QT interval can cause torsade's de pointes.
- Clindamycin predisposes to CDI.

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Antibacterial agents

C. Aminoglycosides and spectinomycin :-

➢ Aminoglycosides :-

- Are effective mainly in Gram-negative infections.
- ommonly used in regimens for intra-abdominal infection.
- Some aminoglycosides, e.g. amikacin, are important components of therapy for MDR-TB.
- Act synergistically with β-lactam antibiotics they are used in combinations to treat infective endocarditis and orthopedic implant infections.
- Oto- and nephrotoxicity must be avoided by monitoring of renal function and drug levels and by use of short treatment regimens.

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Antibacterial agents

C. Aminoglycosides and spectinomycin :-

➢ Spectinomycin :-

- Chemically similar to the aminoglycosides and given intramuscularly.
- Used to treat strains of *Neisseria gonorrhoeae* resistant to β-lactam antibiotics.
- Resistance to spectinomycin is very common.
- Only indication is the treatment of gonococcal urethritis in pregnancy or in patients allergic to β-lactam antibiotics.

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Antibacterial agents

C. Aminoglycosides and spectinomycin :-

❑ Pharmacokinetics

- Negligible oral absorption.
- Hydrophilic, so excellent penetration to extracellular fluid in body cavities.
- Very poor intracellular penetration, negligible CSF and corneal penetration.
- Peak plasma levels 30 minutes after infusion.
- Monitoring of therapeutic levels required.

Antibacterial agents

C. Aminoglycosides and spectinomycin :-

❑ Adverse effects

- Renal toxicity (usually reversible) accentuated by other nephrotoxic agents.

- Cochlear toxicity (permanent) more likely in older people.

- Neuromuscular blockade after rapid intravenous infusion (potentiated by calcium channel blockers, myasthenia gravis and hypomagnesaemia).

❖ *Gentamicin dosing :-*

- Gentamicin is administered at 7 mg/kg body weight.
- In streptococcal and enterococcal endocarditis, commonly used doses are 1 mg/kg 2–3 times daily for enterococcal endocarditis and 3 mg/kg once daily for most strains of oral streptococci.

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Antibacterial agents

D. Quinolones and fluoroquinolones :-

- Are effective and generally well-tolerated bactericidal agents.
- The quinolones have purely anti-Gram-negative activity.
- The fluoroquinolones are broad-spectrum agents.
- Ciprofloxacin has anti-pseudomonas activity but resistance emerges rapidly.
- Quinolones and fluoroquinolones are used for a variety of common infections, including UTI and pneumonia, and less common problems like MDR-TB.

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Antibacterial agents

D. Quinolones and fluoroquinolones :-

Agent	Route of administration	Typical antimicrobial spectrum
Quinolones Nalidixic acid	Oral	Enteric Gram-negative bacilli (not *Pseudomonas aeruginosa*)
Fluoroquinolones		
Ciprofloxacin	IV/oral	Enteric Gram-negative bacilli, *P. aeruginosa*, *Hemophilus* spp., 'atypical' respiratory pathogens
Norfloxacin	Oral	
Ofloxacin	IV/oral/topical	
Levofloxacin	IV/oral	*Hemophilus* spp., *Strep. pneumoniae*, 'atypical' respiratory Pathogens
Moxifloxacin	Oral	*Strep. pneumoniae*, *Staph. aureus*, 'atypical' respiratory pathogens*, Mycobacteria and anaerobes

Antibacterial agents

D. Quinolones and fluoroquinolones :-

❑ Pharmacokinetics:-

- **Well absorbed after oral administration but delayed by food, antacids, ferrous sulphate and multivitamins.**
- **Wide volume of distribution; tissue concentrations twice those in serum.**
- **Good intracellular penetration, concentrating in phagocytes.**

Antibacterial agents

D. Quinolones and fluoroquinolones :-

❑ Adverse effects :-

- ✓ Gastrointestinal side-effects in 1–5%.
- ✓ Rare skin reactions (phototoxicity).
- ✓ Tendinitis and Achilles tendon rupture, especially in older people.
- ✓ Central nervous system effects (delirium, tremor, dizziness and occasional seizures in 5–12%), especially in older people.
- ✓ Reduces clearance of xanthine's and theophylline's, potentially inducing insomnia and increased seizure potential.
- ✓ Prolongation of QT interval on ECG, cardiac arrhythmias.

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Antibacterial agents

E. Glycopeptides :-

- (vancomycin and teicoplanin) are effective against Gram-positive organisms only, and are used against MRSA and ampicillin-resistant enterococci.
- Some staphylococci and enterococci demonstrate intermediate sensitivity or resistance.
- Vancomycin use should be restricted to limit emergence of resistant strains.
- Neither drug is absorbed after oral administration but vancomycin is used orally to treat CDI.

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Antibacterial agents

E. Glycopeptides :-

❑ Pharmacokinetics :-

- ***Vancomycin a*dministered by slow intravenous infusion, good tissue distribution and short half-life.**
- **Enters the CSF only in the presence of inflammation and may require intrathecal administration during neurosurgical infections.**
- **Therapeutic monitoring of intravenous vancomycin is recommended, to maintain pre-dose levels of > 10 mg/L (15–20 mg/L in serious staphylococcal infections).**

❑ Adverse effects :-

- **Histamine release due to rapid vancomycin infusion produces a ‘red man’ reaction (rare with modern preparations).**
- **Nephrotoxicity is rare but may occur with concomitant aminoglycoside use, as may ototoxicity.**

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Antibacterial agents

F. Lipopeptides :-

- Daptomycin is a cyclic lipopeptide with bactericidal activity against Gram-positive organisms (including MRSA) but not Gram-negatives.
- Not absorbed orally, and is used intravenously to treat Gram-positive infections.
- Daptomycin is not effective for community-acquired pneumonia.
- Can be associated with increased levels of CK and eosinophilic pneumonitis.

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Antibacterial agents

G. Polymyxins :-

- Colistin is a polymyxin antibiotic that binds and disrupts the outer cell membrane of Gram-negative bacteria, including *P. aeruginosa* and *Acinetobacter baumannii*.
- Its use has increased with the emergence and spread of multi-resistant Gram-negative bacteria.
- Can be administered by oral, intravenous and nebulized routes.
- Significant adverse effects include neurotoxicity, including encephalopathy, and nephrotoxicity.

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Antibacterial agents

H. Folate antagonists :-

- Bacteriostatic antibacterial.
- A combination with either trimethoprim or pyrimethamine is most commonly used.
- Combinations include trimethoprim/sulfamethoxazole (co-trimoxazole) and pyrimethamine with either sulfadoxine (used to treat malaria) or sulfadiazine (used in toxoplasmosis).
- Co-trimoxazole is the first-line drug for *Pneumocystis jirovecii* infection, the second-line drug for treatment and prevention of *B. pertussis* (whooping cough) infection.
- Also used for a variety of other infections, including *Staph. aureus*.
- Dapsone is used to treat leprosy and to prevent toxoplasmosis and pneumocystis when patients are intolerant of other medications.
- Folic acid should be given to prevent myelosuppression if these drugs are used long-term or unavoidably in early pregnancy.

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Antibacterial agents

H. Folate antagonists :-

❑ Pharmacokinetics :-

- Well absorbed orally.
- Sulphonamides are hydrophilic, distributing well to the extracellular fluid.
- Trimethoprim is lipophilic with high tissue concentrations.

❑ Adverse effects :-

- Trimethoprim is generally well tolerated, with few adverse effects.
- Sulphonamides and dapsone may cause hemolysis in G6PD deficiency.
- Sulphonamides and dapsone cause skin and mucocutaneous reactions, including S-J syndrome and ‘dapsone syndrome’ (rash, fever and lymphadenopathy).
- Dapsone causes methemoglobinemia and peripheral neuropathy.

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Antibacterial agents

I. Tetracyclines and glycylcyclines :-

❖ Tetracyclines

- Mainly bacteriostatic class.
- Newer drugs doxycycline and minocycline show better absorption and distribution than older ones.
- Many streptococci and Gram-negative bacteria are now resistant.
- Tetracyclines are indicated for *Mycoplasma* spp., *Chlamydia* spp., *Rickettsia* spp., *Coxiella* spp., *Bartonella* spp., *Borrelia* spp., *Helicobacter pylori*, *Treponema pallidum* and atypical mycobacterial infections.
- Tetracyclines can also be used for malaria prevention.

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Antibacterial agents

I. Tetracyclines and glycylcyclines :-

- **Glycylcyclines (tigecycline)**
  - **Tigecycline, a broad-spectrum.**
  - **Parenteral-only antibiotic with activity against resistant Gram-positive and Gram-negative pathogens, such as MRSA.**
  - **Have excess mortality, so tigecycline should be used only when there has been adequate assessment of risk versus benefit.**

Antibacterial agents

I. Tetracyclines and glycylcyclines :-

❑ Pharmacokinetics

- Best oral absorption is in the fasting state (doxycycline is 100% absorbed unless gastric pH rises).
- Absorption is inhibited by cations, e.g. calcium or iron.

❑ Adverse effects

- All tetracyclines except doxycycline are contraindicated in renal failure.
- Dizziness with minocycline.
- Binding to metallic ions in bones and teeth causes discoloration.
- Avoid in children and pregnancy.
- Esophagitis/esophageal ulcers with doxycycline.
- Phototoxic skin reactions.

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Antibacterial agents

J. Nitroimidazoles :-

- Nitroimidazoles are highly active against strictly anaerobic bacteria, especially *Bacteroides fragilis*, *C. difficile* and other *Clostridium* spp.
- Have significant antiprotozoal activity against amoebae and *Giardia lamblia*.

❑ Pharmacokinetics

- Almost completely absorbed after oral administration (60% after rectal administration).
- Well distributed, especially to brain and CSF.
- Safe in pregnancy.

❑ Adverse effects

- Metallic taste (dose-dependent).
- Severe vomiting if taken with alcohol – 'Antabuse effect'.
- Peripheral neuropathy with prolonged use.

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Antibacterial agents

K. Phenicol's :-

- Chloramphenicol is the only example in clinical use.
- Its use tends to be reserved for severe and life-threatening infections when other antibiotics are either unavailable, because of concerns about toxicity.
- Is bacteriostatic to most organisms but apparently bactericidal to H. *influenzae*, *Strep. pneumoniae* and *N. meningitidis*.
- Has a very broad spectrum of activity against aerobic and anaerobic organisms, spirochetes, *Rickettsia*, *Chlamydia* and *Mycoplasma* spp.

Antibacterial agents

K. Phenicol's :-

- It competes with macrolides and lincosamides for ribosomal binding sites, so should not be used in combination with these agents.
- Significant adverse effects are 'grey baby' syndrome in infants (cyanosis and circulatory collapse due to inability to conjugate drug and excrete the active form in urine).
- Reversible dose-dependent bone marrow depression in adults receiving high cumulative doses,
- Severe aplastic anemia (unrelated to dose, duration of therapy or route of administration.

Antibacterial agents

L. Oxazolidinones :-

- Linezolid and tedizolid are examples.
- Good activity against Gram-positive organisms.
- Often used to treat skin and soft tissue infections.
- Used in infection caused by resistant Gram-positive bacteria, including MRSA.
- Administration can be intravenous or oral.
- Common linezolid adverse effects include mild G.I.T upset and tongue discoloration.
- Myelodysplasia and peripheral and optic neuropathy can occur with prolonged use.
- Linezolid has (MAOI) activity, and co-administration with other MAOIs or serotonin re-uptake inhibitors should be avoided.

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Antibacterial agents

M. Other antibacterial agents :-

❖ Fusidic acid :-

- Active against Gram-positive bacteria.
- Is available in intravenous, oral or topical formulations.
- Is lipid-soluble and distributes well to tissues.
- Fusidic acid is used in combination, typically with ant staphylococcal penicillin's, or for MRSA with clindamycin or rifampicin.
- It interacts with coumarin derivatives and oral contraceptives.

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Antibacterial agents

M. Other antibacterial agents :-

❖ Nitrofurantoin :-

- Has very rapid renal elimination.
- Active against aerobic Gram-negative and Gram-positive bacteria.
- Only used for treatment of UTI, being generally safe in pregnancy and childhood.
- In prolonged treatment, it can cause eosinophilic lung infiltrates, fever, pulmonary fibrosis, peripheral neuropathy, hepatitis and hemolytic anemia.

❖ Fidaxomicin :-

- Fidaxomicin is an inhibitor of RNA synthesis
- Used for the treatment of non-severe CDI, and is associated with a lower recurrence rate.
- Its effectiveness has not been assessed in severe CDI.

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Antibacterial agents

M. Other antibacterial agents :-

❖ Fosfomycin :-

- Fosfomycin acts by inhibiting cell wall synthesis.
- Activate against Gram-negative but also Gram-positive bacteria.
- Synergy against MRSA when combined with other antimicrobials.
- Used for treatment of urinary tract infections.
- Can be employed in other situations against multi-resistant bacteria.

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Antibacterial agents

M. Other antibacterial agents :-

- **Anti-mycobacterial agents :-**

- **Isoniazid**

- **Is bactericidal for replicating bacteria and bacteriostatic for non-replicating bacteria.**

- **Isoniazid is well absorbed orally and metabolized by acetylation in the liver.**

- **The major side-effects are hepatitis, neuropathy and hypersensitivity reactions.**

Antibacterial agents

M. Other antibacterial agents :-

❖ Anti-mycobacterial agents :-

- **Ethambutol**

➢ **Is a bacteriostatic agent, and It inhibits arabinosyl transferase.**

➢ **Resistance is usually seen when resistance to other antimycobacterial agents.**

➢ **Orally absorbed but, it achieves poor CSF penetration and is renally excreted.**

➢ **The major side-effect is optic neuritis with loss of red–green color discrimination and impaired visual acuity.**

➢ **Can cause hepatitis.**

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Antibacterial agents

M. Other antibacterial agents :-

- **Anti-mycobacterial agents :-**
  - **Rifampicin**

- **Inhibits DNA-dependent RNA polymerase and is bactericidal against replicating bacteria.**
- **Active in necrotic foci, where mycobacteria have low levels of replication.**
- **Important in sterilization and sputum conversion.**
- **Resistance most often occurs with isoniazid-resistant MDR-TB.**
- **Rifampicin is well absorbed orally.**
- **Metabolized by the liver via the microsomal cytochrome P450 system.**

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Antibacterial agents

M. Other antibacterial agents :-

- **Anti-mycobacterial agents :-**
  - **Rifampicin**
    - Subject to extensive drug–drug interactions.
    - Common side-effects include hepatitis, influenza-like symptoms and hypersensitivity reactions.
    - Orange discoloration of urine and body secretions is expected.
  - **Streptomycin**
    - Is an aminoglycoside.
    - The mechanism of action and side-effects are similar to those of other aminoglycosides.
    - Administered intramuscularly.

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Antibacterial agents

M. Other antibacterial agents :-

- **Anti-mycobacterial agents :-**
  - **Pyrazinamide**

- **The mechanism of action of pyrazinamide is incompletely defined but includes inhibition of fatty acid synthase and ribosomal trans-translation.**

- **Often bacteriostatic but can be bactericidal and is active against semi dormant bacteria in a low-pH environment.**

- **Primary resistance is rare but MDR-TB strains are frequently.**

- **Pyrazinamide is well absorbed orally and metabolized by the liver.**

- **Side-effects include nausea, hepatitis, elevation of uric acid and myalgia.**

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Antibacterial agents

M. Other antibacterial agents :-

❖ Other Anti-mycobacterial agents :-

➢ **Second-line agents :-** Used in MDR or XDR strains include :-

- ✓ Aminoglycosides (amikacin, capreomycin or kanamycin).
- ✓ Fluoroquinolones (moxifloxacin or levofloxacin).

➢ **Other second-line agents** administered orally are :-

- ✓ Cycloserine (which causes neurological side-effects).
- ✓ Ethionamide or protionamide have reasonable CSF penetration.
- ✓ The side-effect includes gastrointestinal disturbance, hepatotoxicity and neurotoxicity.
- ✓ Paraminosalicylic acid (which causes rashes and gastrointestinal upset).
- ✓ Linezolid may also be used and has good CSF penetration.
- ✓ Meropenem with co-amoxiclav is occasionally chosen.

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Antibacterial agents

M. Other antibacterial agents :-

❖ **Other Anti-mycobacterial agents :-**

➢ **New drugs developed for XDR-TB include :-**

✓ **Delamanid and bedaquiline.**

- **The adverse effects include QT prolongation and cardiac arrhythmias.**

- **Requires careful risk assessment when co-administration with other agents with a similar side-effect profile (e.g. fluoroquinolones).**

❖ **Clofazimine**

➢ **Clofazimine is used against M. leprae and resistant strains of M. tuberculosis.**

➢ **Its mode of action may involve induction of oxidative stress and it is weakly bactericidal.**

➢ **Oral absorption is variable and it is excreted in the bile.**

➢ **Side-effects include gastrointestinal upset, dry eyes and skin, and skin pigmentation, especially in those with pigmented skin.**

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Antibacterial agents

❖ SELECTED PRINCIPLES OF ANTIMICROBIAL THERAPY :-

➢Specific steps are required when considering antibiotic therapy for patients.

A. Etiologic Diagnosis

➢Based on the organ system involved, the organism causing infection.

B. "Best Guess"

➢Select an empiric regimen that is likely to be effective against the suspected pathogens.

C. Laboratory Control

➢Specimens for laboratory examination should be obtained before institution of therapy to determine susceptibility.

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Antibacterial agents

❖ **SELECTED PRINCIPLES OF ANTIMICROBIAL THERAPY :-**

D. Clinical Response

➢Based on clinical response and other data, the laboratory reports.

➢The recovery of a microorganism in significant amounts is meaningful even if the organism recovered is different from the clinically suspected agent, and this may force a change in treatment.

➢Isolation of unexpected microorganisms from the sites that have a complex flora) may represent colonization or contamination, and cultures must be critically evaluated before drugs are abandoned that were judiciously selected on a "best guess" basis.

Antibacterial agents

❖ **SELECTED PRINCIPLES OF ANTIMICROBIAL THERAPY :-**

E. Drug Susceptibility Tests

- Some microorganisms are predictably inhibited by certain drugs; if such organisms are isolated, they need not be tested for drug susceptibility.

- Other organisms are variably susceptible and generally require susceptibility testing whenever they are isolated.

- Organisms that once had predictable susceptibility patterns have now become resistant and require testing.

- When culture and susceptibility results have been finalized, it is important to utilize the most narrow spectrum agent possible to decrease the selection pressure for antibacterial resistance.

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Antibacterial agents

❖ SELECTED PRINCIPLES OF ANTIMICROBIAL THERAPY :-

E. Drug Susceptibility Tests

- When marked discrepancies between susceptibility testing and clinical response, the following possibilities must be considered:

1. Selection of an inappropriate drug, drug dosage, or route of administration.

2. Failure to drain a collection of pus or to remove a foreign body.

3. Failure of a poorly diffusing drug to reach the site of infection (egg, CNS) or to reach intracellular phagocytosed bacteria.

4. Superinfection in the course of prolonged chemotherapy.

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Antibacterial agents

❖ SELECTED PRINCIPLES OF ANTIMICROBIAL THERAPY :-

E. Drug Susceptibility Tests

5. Emergence of drug-resistant organisms.

6. Participation of two or more microorganisms in the infectious process, of which only one was originally detected and used for drug selection.

7. Inadequate host defenses, including immunodeficiencies and diabetes mellitus.

8. Noninfectious causes, including drug fever, malignancy, and autoimmune disease.

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Antibacterial agents

❖ **SELECTED PRINCIPLES OF ANTIMICROBIAL THERAPY :-**

F. Promptness of Response

- Response depends on a number of factors, including :-
  - The patient (immunocompromised patients respond slower than immunocompetent patients), the site of infection, the pathogen and the duration of illness.
  - The clinical situation, persistent fever and leukocytosis several days after initiation of therapy may not indicate improper choice of antibiotics but may be due to the natural history of the disease being treated.
- In most infections, either a bacteriostatic or a bactericidal agent can be used.

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Antibacterial agents

❖ SELECTED PRINCIPLES OF ANTIMICROBIAL THERAPY :-

F. Promptness of Response

- In some infections (egg, IE and meningitis), a bactericidal agent should be used.

- potentially toxic drugs (eg, aminoglycosides, flucytosine) are used, serum levels of the drug are measured to minimize toxicity and ensure appropriate dosage.

- In elderly, obese patients, and patients with altered renal or hepatic clearance of drugs, the dosage or frequency of administration must be adjusted.

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Antibacterial agents

❖ **SELECTED PRINCIPLES OF ANTIMICROBIAL THERAPY :-**

G. Duration of Antimicrobial Therapy

- Generally, effective antimicrobial treatment results in reversal of the clinical and laboratory parameters of active infection and marked clinical improvement.

- Varying periods of treatment may be required for cure.

❖ **Key factors include**

(1) the type of infecting organism (bacterial infections generally can be cured more rapidly than fungal or mycobacterial ones).

(2) the location of the process (eg, endocarditis and osteomyelitis require prolonged therapy).

(3) the immunocompetence of the patient.

DR \ Nashwan Mansoor

Antibacterial agents

❖ SELECTED PRINCIPLES OF ANTIMICROBIAL THERAPY :-

H. Adverse Reactions and Toxicity

- Include hypersensitivity reactions, direct toxicity, superinfection by drug-resistant microorganisms, and drug interactions.
- In life threatening infection and treatment cannot be stopped, the reactions are managed symptomatically or another drug is chosen that does not cross-react with the offending one .
- In less serious infection , it may be possible to stop all antimicrobials and monitor the patient closely.

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Antibacterial agents

❖ **SELECTED PRINCIPLES OF ANTIMICROBIAL THERAPY :-**

I. Route of Administration

- Intravenous therapy is preferred for acutely ill patients with serious infections when dependable levels of antibiotics are required for successful therapy.

- Certain drugs (eg, fluconazole, voriconazole, rifampin, metronidazole, TMPSMZ, and fluoroquinolones) are so well absorbed that they generally can be administered orally in seriously ill, but not hemodynamically unstable patients.

- Food does not significantly influence the bioavailability of most oral antimicrobial agents.

- The tetracyclines and the quinolones chelate multivalent cations resulting in decreased antibacterial absorption.

Antibacterial agents

❖ **SELECTED PRINCIPLES OF ANTIMICROBIAL THERAPY :-**

I. Route of Administration

- Azithromycin capsules are associated with decreased bioavailability when taken with food and should be given 1 hour before or 2 hours after meals.
- Posaconazole solution should always be administered with food.
- A major complication of intravenous antibiotic therapy is catheter infections.
- Peripheral catheters are changed every 48–72 hours to prevent phlebitis, and infections.
- Central venous catheters have been associated with a decreased incidence of catheter-related infections.

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Antibacterial agents

❖ **SELECTED PRINCIPLES OF ANTIMICROBIAL THERAPY :-**

I. Route of Administration

- Most of these infections present with local signs of infection at the insertion site.
- In a patient with fever who is receiving intravenous therapy, the catheter must always be considered a potential source.
- Small-gauge peripherally inserted silicone or polyurethane catheters are associated with a low infection rate and can be maintained for 3–6 months without replacement.
- Such catheters are ideal for long-term outpatient antibiotic therapy.

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Antibacterial agents

❖ SELECTED PRINCIPLES OF ANTIMICROBIAL THERAPY :-

J. Cost of Antibiotics

- The cost of these agents can be substantial.
- Monitoring costs, (drug levels, liver function tests, electrolytes, etc.).
- The cost of treating adverse reactions.
- The cost of treatment failure.
- The costs associated with drug administration must be considered.

Antibacterial agents

❖ SELECTED PRINCIPLES OF ANTIMICROBIAL THERAPY :-

➢ Antimicrobial agents in pregnancy :-

Contraindicated
• Chloramphenicol: neonatal 'grey baby' syndrome – collapse, hypotension and cyanosis.
• Fluconazole: teratogenic in high doses
• Quinolones: arthropathy in animal studies
• Sulphonamides: neonatal hemolysis and methemoglobinemia
• Tetracyclines, glycylcyclines: skeletal abnormalities in animals in first trimester; fetal dental discoloration and maternal hepatotoxicity with large parenteral doses in second or third trimesters.
• Trimethoprim: teratogenic in first trimester

Antibacterial agents

❖ **SELECTED PRINCIPLES OF ANTIMICROBIAL THERAPY :-**

➢ Antimicrobial agents in pregnancy :-

Relatively contraindicated
• **Aminoglycosides: potential damage to fetal auditory and vestibular nerves in second and third trimesters.**
• **Metronidazole: avoidance of high dosages is recommended**

Antibacterial agents

❖ **SELECTED PRINCIPLES OF ANTIMICROBIAL THERAPY :-**

- Antimicrobial agents in pregnancy :-

Not known to be harmful; use only when necessary		
Acyclovir	**Clindamycin**	**Linezolid**
Cephalosporins	**Erythromycin**	**Meropenem**
Clarithromycin	**Glycopeptides**	**Penicillin's**

Antibacterial agents

❖ **SELECTED PRINCIPLES OF ANTIMICROBIAL THERAPY :-**

➢ Problems with antimicrobial therapy in old age :-

- **Clostridium difficile infection:** all antibiotics predispose to some extent, but second- and third-generation cephalosporins, co-amoxiclav and fluoroquinolones (e.g. ciprofloxacin).

- **Hypersensitivity reactions:** rise in incidence due to increased previous exposure.

- **Renal impairment:** may be significant in old age, despite 'normal' creatinine levels.
- **Nephrotoxicity:** more likely, e.g. first-generation cephalosporins, aminoglycosides.

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Antibacterial agents

❖ **SELECTED PRINCIPLES OF ANTIMICROBIAL THERAPY :-**

➢ Problems with antimicrobial therapy in old age :-

- **Accumulation of β-lactam antibiotics:** may result in myoclonus, seizures or coma.
- **Reduced gastric acid production:** gastric pH is higher, which causes increased penicillin absorption.
- **Reduced hepatic metabolism:** results in a higher risk of isoniazid-related hepatotoxicity.
- **Quinolones:** associated with delirium and may increase the risk of seizures.

DR \ Nashwan Mansoor

Thank you

DR \ Nshwan Mansoor